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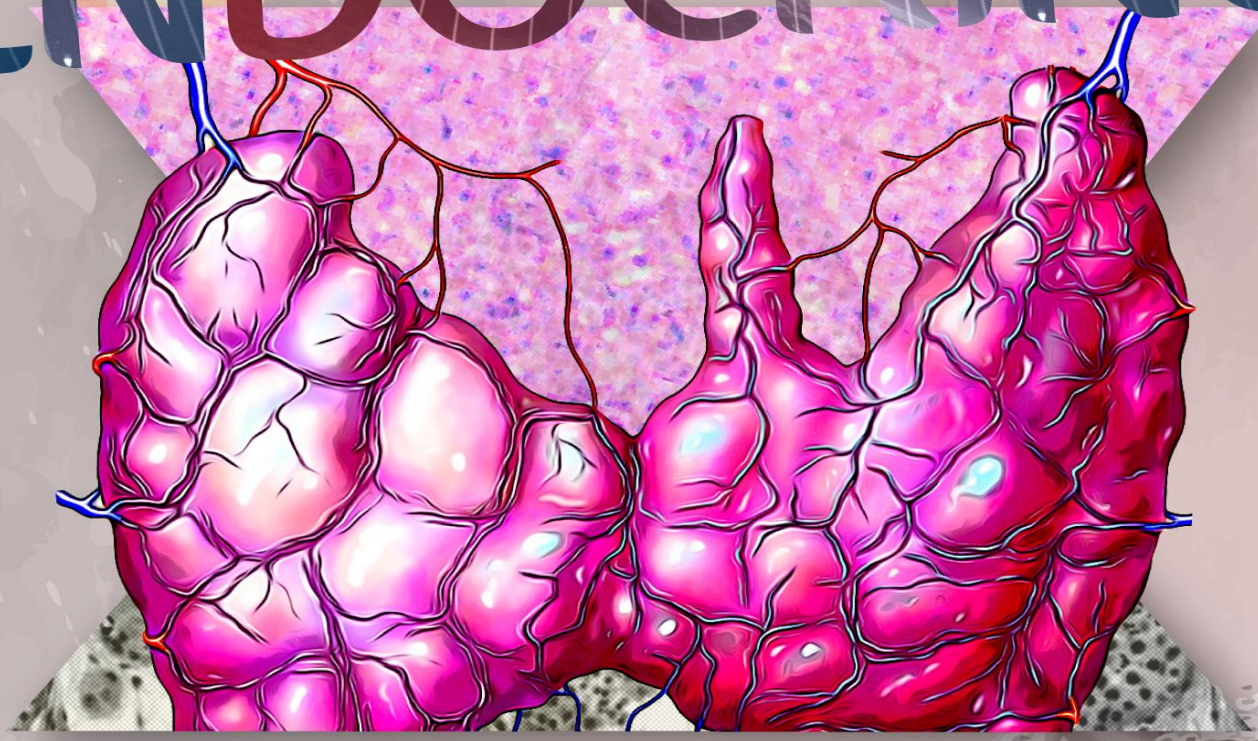

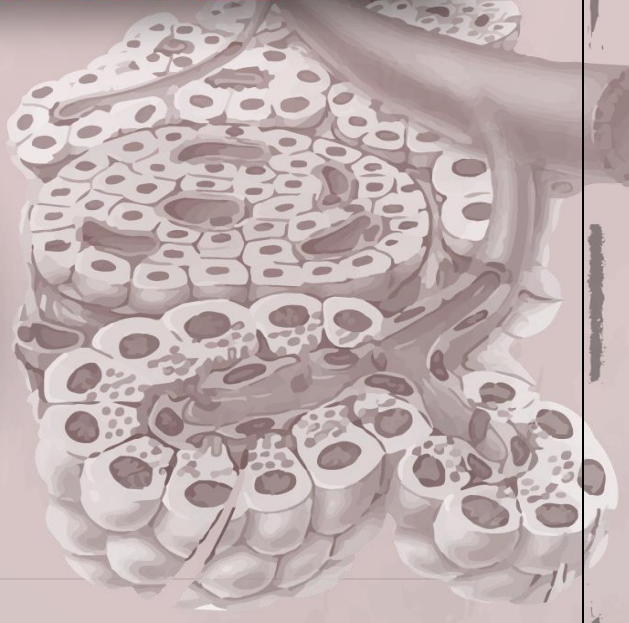

SUBJECT: Physiology

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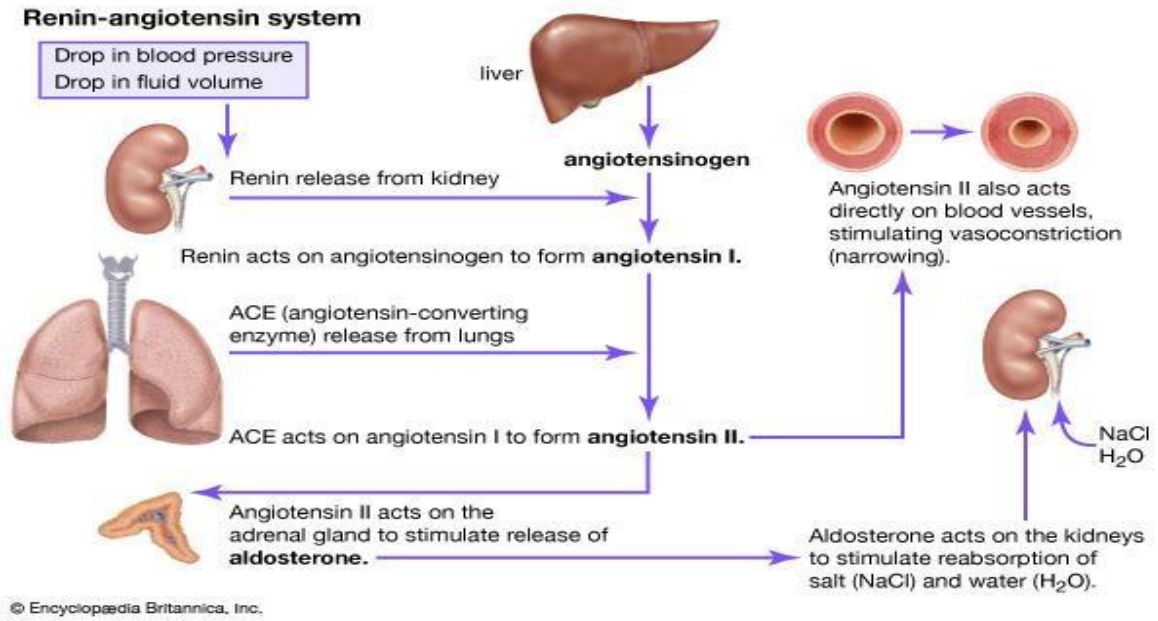
The doctor revise RAS, Aldosterone & Angiotensin II function (mentioned in sheet 4)...New subject starts on page 8

Renin-Angiotensin System (RAS):

The **Renin–Angiotensin System** (**RAS**) or the **Renin–Angiotensin–Aldosterone System** (**RAAS**) is a hormone system that regulates blood pressure and fluid balance. When renal blood flow is reduced, **juxtaglomerular cells in the kidneys** convert the precursor "prorenin" ,which is already present in the blood, into Renin and secrete it directly into the circulation. Plasma Renin then carries out the conversion of **angiotensinogen, that is produced by the liver**, into angiotensin I.

Angiotensin I is subsequently converted to angiotensin II by the angiotensin-converting enzyme **(ACE) found in the lungs**. Angiotensin II is a potent vasoconstrictive peptide that causes blood vessels to narrow, resulting in an increased blood pressure. Angiotensin II also stimulates the secretion of the hormone **Aldosterone** from the **<u>adrenal cortex</u>**. Aldosterone causes the renal tubules to increase the reabsorption of sodium and water into the blood, while at the same time causing the excretion of potassium (to maintain electrolyte balance). This increases the volume of ECF in the body, which also increases blood pressure.



Aldosterone function and mechanism of action:

- Aldosterone is an important regulator of sodium reabsorption and secretion of potassium and hydrogen ions by the renal tubules.

- A major renal tubular site of aldosterone action is the principal cells of the cortical collecting tubules.

1. Because Aldosterone is lipid soluble, it diffuses readily to the interior of the tubular epithelial cells.

2. In the cytoplasm of the tubular cells, Aldosterone combines with a highly specific cytoplasmic **mineralocorticoid receptor (MR)** protein. This receptor also has high affinity for cortisol, the **enzyme 11 β -HSD2** normally converts most of the cortisol to cortisone, which does not readily bind to MR receptors.

3. The Aldosterone-Receptor complex or a product of this complex diffuses into the nucleus, inducing one or more specific portions of the DNA to synthesize one or more types of mRNA related to the process of sodium and potassium transport.

4. The mRNA diffuses back into the cytoplasm causing protein synthesis. The synthesized proteins are a mixture of (1) one or more enzymes (2) membrane-transport proteins that, all acting together, are required for sodium, potassium and hydrogen transport through cell membranes.

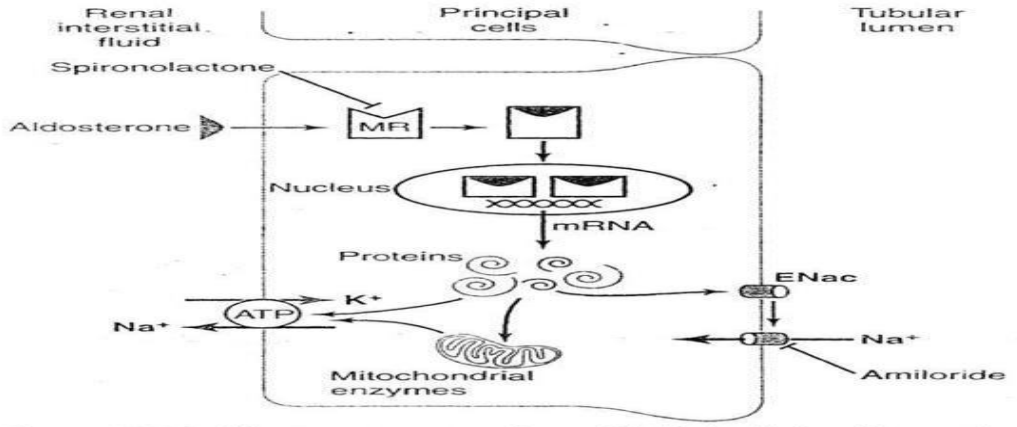


Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

Regulators of aldosterone secretion:

1. Potassium ion concertation.
2. RAS.
3. Increased sodium ion concentration in the ECF slightly decreases Aldosterone secretion.
4. ACTH from the anterior pituitary is necessary for Aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions.

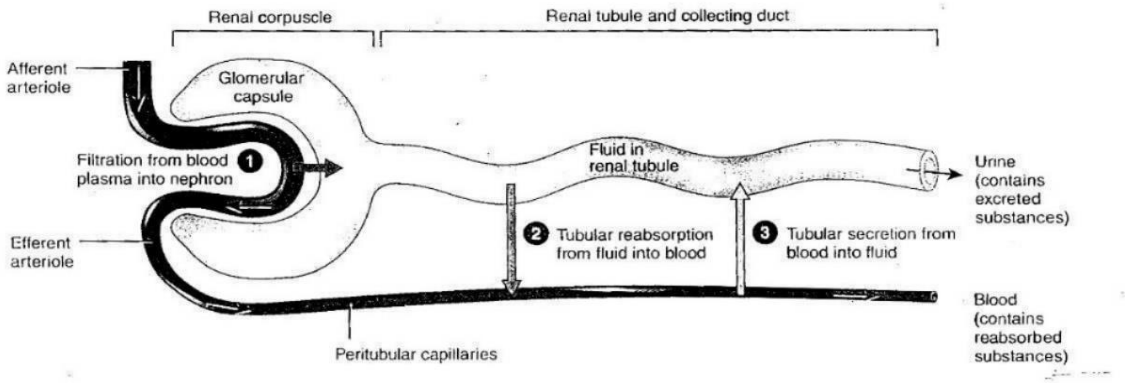
Angiotensin ll function and mechanism of action:

1. Angiotensin ll stimulates aldosterone secretion which in turn increases sodium reabsorption.
2. Angiotensin ll constricts the efferent arterioles, which has two effects on peritubular capillary dynamics that increase sodium and water reabsorption:

Indirect Effect:

I. Efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules.

II. Efferent arteriole constriction reduced renal blood flow, thus increasing the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries; this increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water.



Direct Effect:

III. Angiotensin II directly stimulates sodium reabsorption by stimulating the sodium-potassium ATPase pump on the tubular epithelial cell basolateral membrane of the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules.

IV. It also stimulates sodium-hydrogen exchange in the luminal membrane, especially in the proximal tubule.

3. Angiotensin II stimulates sodium-bicarbonate co-transport in the basolateral membrane.

- Controlling blood pressure and blood volume is mainly stimulated by angiotensin ll (potent vasoconstrictor) which controls aldosterone. Aldosterone does not only function on renal tubules; it also functions on the salivary glands, intestine and sweat glands.

- There are 3 types of angiotensin; angiotensin III is similar to angiotensin II in potency, but it is released in smaller amounts.

- The synthesis of angiotensin II is inhibited by using angiotensin II converting enzyme inhibitors, this will we inhibit the formation of angiotensin II from angiotensin I, thus angiotensin I concentration will increase. These inhibitors are usually safe drugs, but they don't work on every individual so we might depend on other drugs that may have some side effects.

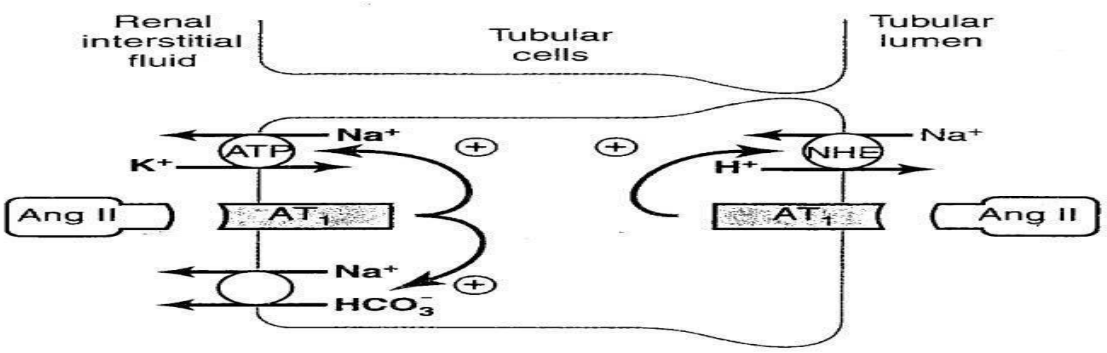


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. These same effects of Ang II likely occur in several other parts of the renal tubule, including the loop of Henle, distal tubule, and collecting tubule.

Androgens and estrogens:

1. They are secreted mainly by the **zona reticularis** of adrenal cortex, and small amounts are secreted by **zona fasciculate** with cortisol.

2. Two weak androgens are produced by zona reticularis: **dehydroepiandrosterone** and **androstenedione**. These androgens produce ***testosterone***, the **most potent** androgen. Testosterone then produces **estradiol** and androstenedione produces **estriol.**

3. Adrenal Androgens & Estrogens aren't that important in males, because testosterone is also produced by the testes. However, they are very important in females in all stages of life, especially after menopause when the ovaries stop functioning.

Actions of Adrenal Androgens:

- In Females: the presence of pubic hair & libido.
- In Males: same as testosterone.

❖ If the synthesis of cortisol is blocked, the level of Corticosteroids increases as well as the level of Androgens.

Thyroid Gland

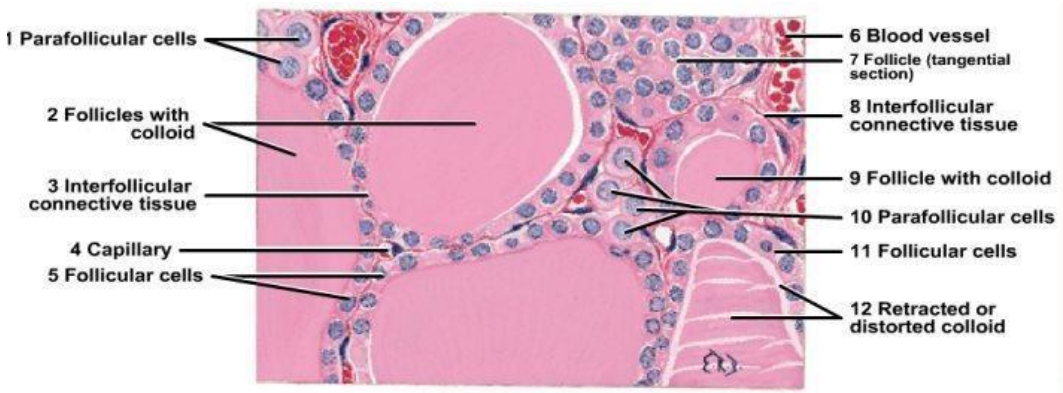
- ✓ It's composed of two lobes: right and left, joined together by a stalk called isthmus. It lies in front of trachea and it has a rich blood supply.

- ✓ At the **12th week** of gestation, the thyroid gland begins to function for the development of all systems, especially **CNS and Skeletal system**. Because maternal thyroid hormones, anterior pituitary hormones and the hypothalamic hormones can't cross the placenta, the fetus must synthesize their own hormones.

- ✓ Note that **thyroid hormones** affect physical and mental growth of the fetus in contrast to the **GH** which only affects the physical growth.

- ✓ When taking a cross section from thyroid gland, you can see follicles lined by cuboidal epithelium. In between the follicles there is *parafollicular cells* that produce the *unrelated hormone "calcitonin"* which functions on decreasing the Ca+ plasma level.

- ✓ The epithelial (follicular) cells secrete **thyroglobulin** into the **colloid,** which is filled with fluid that contains hormones, amino acids, enzymes... Etc.



Physiology of the thyroid gland

- The secretion of thyroid hormones is stimulated by **TSH** (also called **thyrotropin**) from the anterior pituitary which is stimulated by ***TRH*** (thyrotropin releasing hormone) secreted by nerve endings in the median eminence of the hypothalamus.

*Note: TSH is inhibited by the **Dopamine**, **Somatostatin**, **cortisol** and **growth hormone**.*

1. **TRH**: secreted by the *hypothalamus* and stimulates the secretion of TSH by the anterior pituitary. The binding of TRH to its receptors in the pituitary cell membrane activates **phospholipase second messenger system** inside the pituitary cells **to produce phospholipase c** followed by **second messengers as calcium ions and diacylglycerol**, which eventually leads to **TSH release**.

2. **TSH**: stimulates the growth of thyroid gland cells and increases both the synthesis and secretion of thyroid hormones by the follicular cells. TSH binds to **its receptors on the basal membranes** of the thyroid cell. This binding **activates adenylyl cyclase** in the membrane, which increases the **formation of cAMP** inside the cells to stimulate hormones secretion. Another two second messengers stimulated are **DAG & IP3** for the growth of cells of the thyroid gland.

TSH is a *glycoprotein*, and its receptor is on the cell membrane. It is composed of two peptides subunits:

- Alpha (α) subunit: nonspecific because it is also a part of another three unrelated hormones (LH, FSH, CGH).

- Beta (β) subunit is the specific biological active site of the hormone, it differs between TSH & (LH, FSH, CGH). It doesn't function unless it is bound with alpha.

- TRH controls the **Synthesis** and the **Bioactivity** of TSH

Feedback effect of thyroid hormone*: Increased thyroid hormone in body fluids decreases the secretion of: thyroid hormones (themselves), TSH directly from the anterior pituitary & TRH. So, thyroid hormones feedback all steps of the pathway.*

Structure of the thyroid hormones:

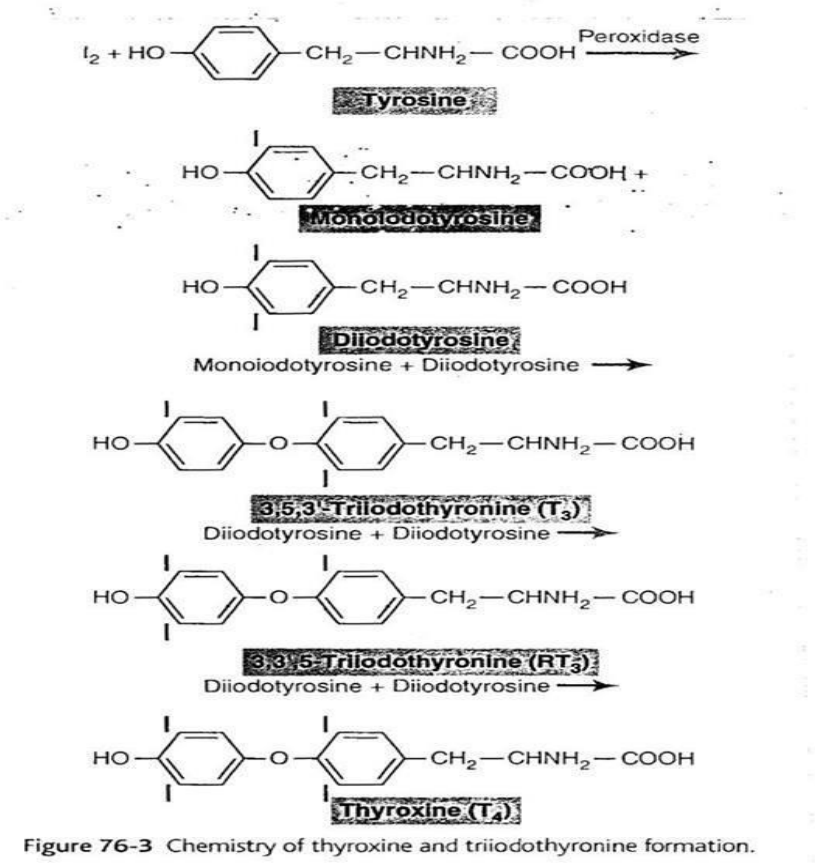


Figure 76-3 Chemistry of thyroxine and triiodothyronine formation.

The thyroid gland produces **iodothyronines** and **iodotyrosine**:

1. Tyrosine with one iodine forms monoiodotyrosine (**MIT**). MIT with another iodine: Diiodotyrosine (**DIT**). This is called **Iodination**.

2. One monoiodotyrosine binds with diiodotyrosine to form triiodothyronine (**T3**) hormone, but when two diiodotyrosine binds; tetraiodothyronine (**T4**) or thyroxine hormone is formed. This is called **Coupling.**

- There is an enzyme that inactivates T3 or T4 to produce inactive hormone called **Reverse T3**. The difference between T3 & reverse T3 is the location of the iodine on the tyrosine, which is ***3, 5, 3*** and ***3, 3, 5*** for T3 and Reverse T3 respectively.

- Tyrosine carries **2 iodine** molecules maximum.
- Thyroid gland produces mainly T4, little T3 (25%), and a little of reverse T3 (5%).
- T4 is the pro-hormone that produces other hormones. The functioning hormone is **T3 (the most active)**, while **T4 is either inactive or has a little activity** and **reverse T3 is totally inactive**.
- Tyrosine is one amino acid and thyronine is two attached tyrosines.
- Iodination is also called organification.

Thyroid gland is **unique** because of two aspects:

1. Incorporation of inorganic substances (**iodine**) with organic substances (**tyrosine**).
2. It is the only gland that stores a lot of hormones inside the colloid. Stored hormones are sufficient for about 2-3 months, which means: if we cut the connection between the thyroid and the pituitary glands, the thyroid gland will be able to secrete hormones for 3 months. Iodine is also stored in the body for about 6 months mainly in the thyroid gland.

synthesis and secretion of thyroid hormones:

- Iodides which are essential for the formation of the hormones are ingested orally then absorbed by the GI tract into the blood. Most of this Iodides are excreted by the kidneys, and about **1/5** of the iodides are taken by the thyroid cells (Blood> interstitial fluid (IF) > thyroid cells). These iodides enter the cells from the IF actively by the sodium-iodide symporter at the basolateral membrane (two sodium ions with one iodide ion). The energy gradient of this co-transport came from previous pumped sodium ions by Na-K ATPase pump. This process of concentrating iodides in the cells is called **iodide trapping**.

- Iodide is transported out of the thyroid cells across **apical membrane** into the follicle by chloride-iodide ion counter-transporter molecule called **pendrin**. The thyroid cells also secret into the follicle *thyroglobulin* that contains tyrosine amino acids to which the iodine will bind. Each molecule contains about 70-130 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the **thyroglobulin** molecule and they remain part of it during synthesis and storage. It means that **iodination and coupling only occur within thyroglobulin, not with free tyrosine.**

- Only about (***4-8)%*** of the amino acids are used to produce thyroid hormones and about **¾** of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remain MIT (monoiodotyrosine) and DIT (diiodotyrosine).

- Before iodination of tyrosine, iodide ions must be oxidized to iodine by the enzyme **peroxidase** and its accompanying hydrogen peroxide, this enzyme is located at the apical membrane of the cell or attached to it.

- After iodination and coupling, thyroglobulin is now carrying (T3, rT3, T4, MIT & DIT) and is transported from the colloid into the cells by **pinocytosis**. Inside the cell, thyroglobulin fuses with lysosomes, and under the effect of enzymes (**proteases**); these hormones become free, then the hormones (T4, T3, rT3) are released into the blood to perform their function.

Metabolism of thyroxine (T4):

- As we said, T4 is a pro-hormone, from which other hormones are synthesized. T4 either produces inactive substances as **reverse T3** or active substances as **T3** & **(DIT)** diiodotyrosine.
  - 75% of T3 comes from T4 → T3 mainly comes from T4.
  - 95% of reverse T3 comes from T4.

The release of T3 & reverse T3 depends on the needs of the body. However, reverse T3 / T3 ratio is always greater than 1.

Thyroid gland questions:

1. Which is false about the thyroid: Iodine deficiency doesn't cause goiter.
2. Which is false about T4: It acts more rapidly than T3.
3. Which is true about thyroglobulin: Contains MIT & DIT.
4. True about Thyroxin synthesis: Iodide (I^-) is oxidized to Iodine (I)
5. Which of the following when found in excess amounts causes protein catabolism: T3.
6. What happens to most of T4? Converted to T3
7. Which of the following doesn't occur in thyroid hormone synthesis: >>> 4 molecules of iodine bind to one molecule of tyrosine to form tetraiodothyronine. (2 molecules).
8. Most abundant thyroid hormone produced is: T4
9. Most potent thyroid hormone produced is: T3